9 Multiple Traits & Multiple Environments

- 2 traits: mechanics (Jiang Zeng 1995)
- close linkage or pleiotropy?
- multiple traits: efficiency beyond 2?
  - principal components on phenotypes
  - discriminant analysis (PC on residuals)
- outbred crosses
  - mixed model approach
  - linkage & linkage disequilibrium

why study multiple traits together?

- avoid reductionist approach to biology
  - address physiological/biochemical mechanisms
  - Schmalhausen (1942); Falconer (1952)
- separate close linkage from pleiotropy
  - 1 locus or 2 linked loci?
- identify epistatic interaction or canalization
  - influence of genetic background
- establish QTL x environment interactions
- decompose genetic correlation among traits
- increase power to detect QTL

why are traits correlated?

- environmental correlation
  - non-genetic, controllable by design
  - historical correlation (learned behavior)
  - physiological correlation (same body)
- pleiotropy
  - one gene, many functions
  - common biochemical pathway, splicing variants
- close linkage
  - two tightly linked genes
  - genotypes *Q* are collinear

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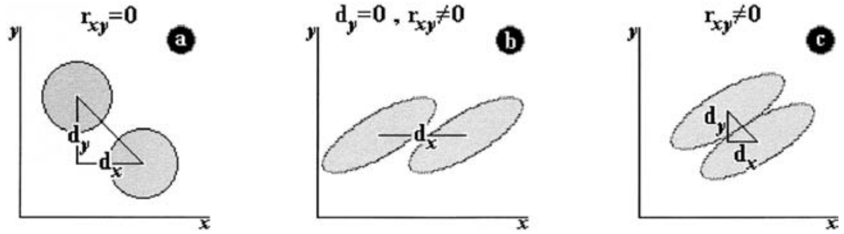
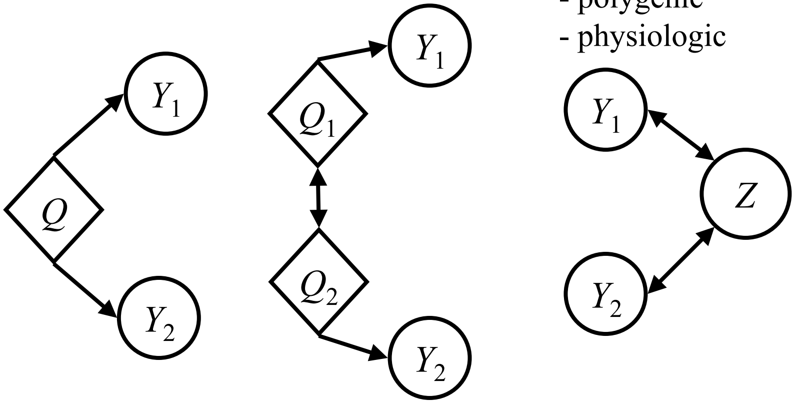
interplay of pleiotropy & correlation



pleiotropy only correlation only both

Korol et al. (2001)

path diagrams (errors omitted)



pleiotropy

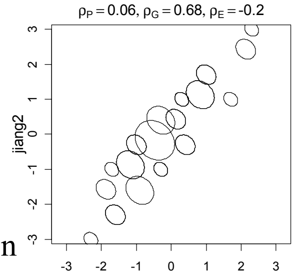
close linkage

other correlation
- polygenic
- physiologic

QTL affecting multiple traits

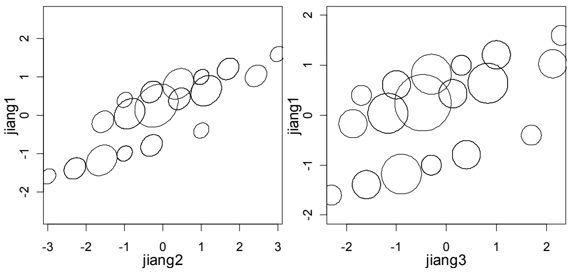
- typical tests at a locus
  - is there a QTL here for any trait?
  - same QTL effect across traits or environments?
- power for single trait vs. multiple trait models
- Haley-Knott regression approach
  - Knott Haley (2000) simulated data
- IM & CIM approach
  - Jiang Zeng (1995); Korol et al. (1995) simulated data
  - Vieira et al. (2000) *Drosophila* lifespan

3 correlated traits (Jiang Zeng 1995)



ellipses centered on genotypic value
width for nominal frequency
main axis angle environmental correlation
3 QTL, F2
27 genotypes

note signs of genetic and environmental correlation



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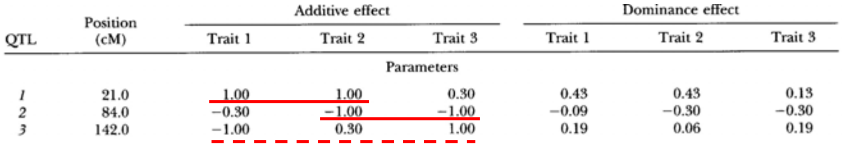
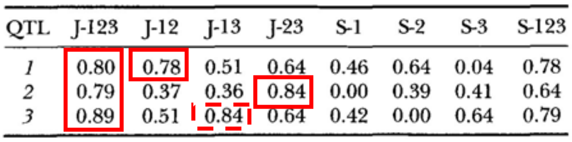
power: separate analysis vs. multiple trait analysis



QTL	Position (cM)	Additive effect			Dominance effect		
		Trait 1	Trait 2	Trait 3	Trait 1	Trait 2	Trait 3
Parameters							
1	21.0	1.00	1.00	0.30	0.43	0.43	0.13
2	84.0	−0.30	−1.00	−1.00	−0.09	−0.30	−0.30
3	142.0	−1.00	0.30	1.00	0.19	0.06	0.19

TABLE 5

Observed statistical power (proportion of significant replicates over all replicates) of seven methods of QTL mapping from 100 replicates of simulations



QTL	J-123	J-12	J-13	J-23	S-1	S-2	S-3	S-123
1	0.80	0.78	0.51	0.64	0.46	0.64	0.04	0.78
2	0.79	0.37	0.36	0.84	0.00	0.39	0.41	0.64
3	0.89	0.51	0.84	0.64	0.42	0.00	0.64	0.79

history: pleiotropy vs. close linkage

- Schork et al. (1994)
- single trait analyses
  - Cheverud et al. (1997); Lebreton et al. (1998)
  - may lack power
- outbred
  - Almasy et al. (1997)
  - bivariate: unclear how to extend to multivariate
- multiple trait regression
  - Knott, Haley (2000)
  - easily extensible, fast
  - reasonable power, concerns about approx (Kao 2000)

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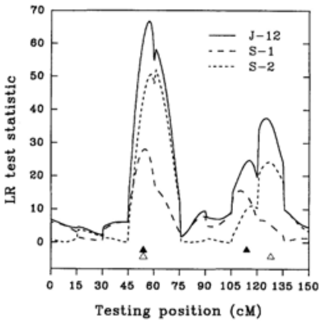
pleiotropy or close linkage?

2 traits, 2 qtl/trait
pleiotropy @ 54cM
linkage @ 114,128cM
Jiang Zeng (1995)



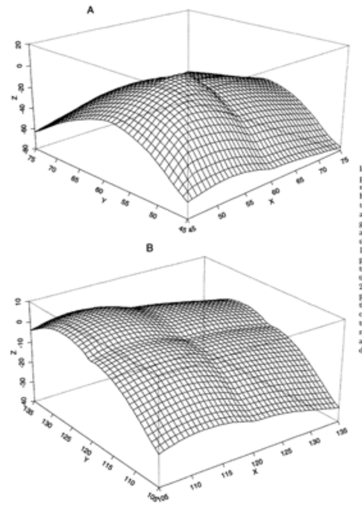
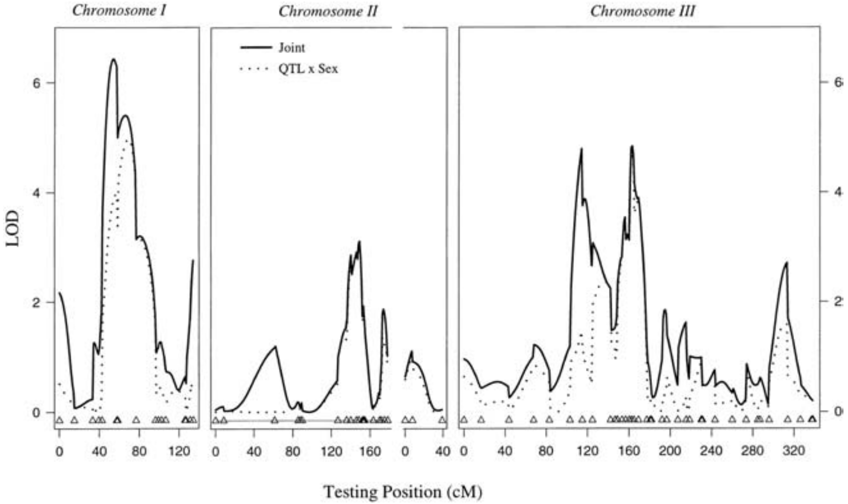
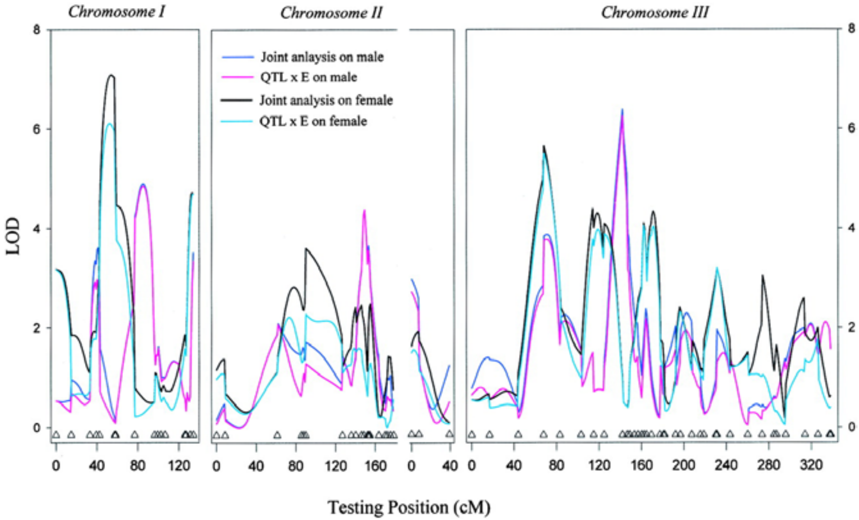


FIGURE 2.—Two-dimensional log-likelihood surfaces (expressed as deviations from the maximum of the log-likelihoods on the diagonal) for the test of pleiotropy *vs.* close linkage are presented for two regions: the region between 45 and 75 cM of Figure 1 (A) and the region between 105 and 135 cM (B). *X* is the testing position for a QTL affecting trait 1 and *Y* is the testing position for a QTL affecting trait 2. On the diagonal of *X*-*Y* plane, two QTL are located in the same position and statistically are treated as one pleiotropic QTL. *Z* is the likelihood ratio test statistic scaled to zero at the maximum point of the diagonal.

QTL x sex interaction (Vieira et al. 2000)



QTL x environment interaction (Vieira et al. 2000)



generalizing heritability to multiple traits

- multivariate normal model: Y_i = vector of t traits
  - $Y_i = \mu + G_i(Q) + e_i,\ e_i \sim MVN(0, V_{\mathrm{E}})$
- partition trait variance-covariance matrix
  - $V_{\mathrm{TOT}} = V_{\mathrm{G}} + V_{\mathrm{E}}$
- determinant of V generalizes variance
  - $| V | = \det(V)$
  - $H^2 = | V_{\mathrm{G}} | / | V_{\mathrm{TOT}} |$
  - maximize H^2 by minimizing $| V_{\mathrm{E}} |$
- use in weighted least squares (or LOD)
  - Korol et al. (1995); Knott, Haley (2000); Korol et al. (2001)

QTL via Principal Components

- PC or SVD decomposition of multiple traits
  - $Y = n \times t$ matrix: $Y = UDU^{\mathrm{T}}$
  - U = orthonormal transformation
  - D = diagonal matrix with eigen-values
- transform problem to principal components
  - $Y^* = FY$ has uncorrelated PC traits ($F = D^{-1/2}U^{\mathrm{T}}$)
  - $Y^* = \mu^* + G^*_Q + e^*$
- interval map each PC separately
  - $Y^*_{1i} = \mu^*_{1i} + G^*_1(Q_i) + e^*_{1i}$
  - may only need to map a few PCs

QTL via Principal Components

- example: *Drosophila* reproduction
  - Liu et al. (1996); Zeng et al. (2000); ch. 7
- other refs
  - Weller et al. (1996); Mangin et al. (1998); Olson et al. (1999); Mahler et al. (2002)
- problems
  - PC may have no relation to genetics!
  - residuals from QTL correlated across PCs
  - PC is descriptive summary, not interpretive

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interval-dependent PC

- want to reduce dimensionality while focusing on QTL differences
- interval-dependent PC on residuals
  - reduces dimensionality by identifying patterns in residuals not explained by QTL
  - not quite discriminant analysis: does not aim to best discriminate among QTL genotypes
- pleiotropy highlighted by PCs
  - find strongest correlation
  - interval map using transformed data
- Allison et al. (1998); Korol et al. (2001)

interval-dependent PC details

- flanking marker based PC
  - remove effect of flanking markers (Haley-Knott)
  - PC decomposition of residuals
  - transform original data to new PC axes
  - map transformed data on interval
  - problem: bias, variance for Haley-Knott
- improvement through iteration
  - PC decomposition of residuals of transformed data
  - repeat until estimates stabilize

LOD depends on number of traits

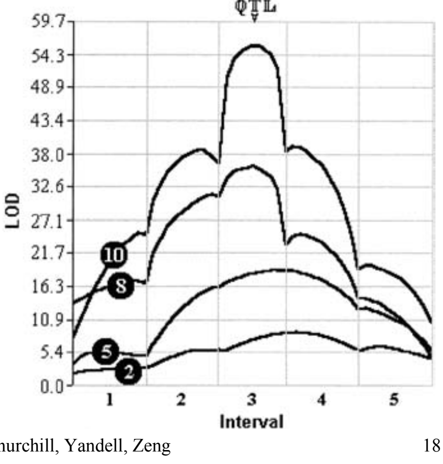
- higher, steeper LOD
  - more power
  - provided traits are correlated
- simulated data (BC)

  $n = 200$

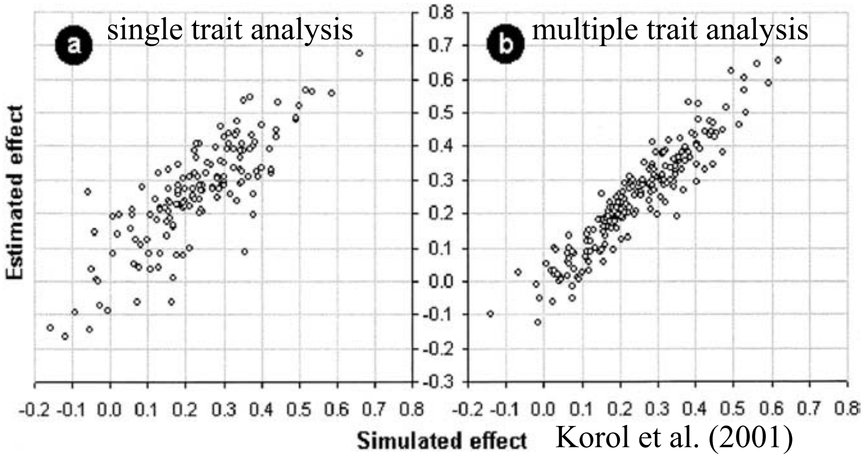
  $t = 2,5,8,10$

  $h^2 = .072,.173,.254,.294$

Korol et al. (2001)



power of multiple trait analysis estimated effect of 1 QTL



single trait analysis

multiple trait analysis

Korol et al. (2001)

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multiple traits for outbred crosses

- Almasy et al. (1997); Lund et al. (2003)
- recombination model blends linkage and linkage disequilibrium (recall ch. 8)
- limited implementation
  - single QTL
  - proof of principle

outbred mixed model: multiple traits

- phenotypes = design + QTLs + polygenes + env
  - $Y = \mu + G_Q + g + e$
  - $Y_{ij} = \mu_j + G_j(Q_i) + g_{ij} + e_{ij}$, $i = 1,\ldots,n$, $j = 1,\ldots,t$
- QTL effects: fixed or random
- random polygenic effects
  - within trait correlation depends on relationship A
  - between trait polygenic correlations?
- random environmental errors
  - correlation among traits unexplained by polygenes

$$g_{\bullet j} \sim MVN(0, W_{jj}A), \text{ or } \mathrm{cov}(g_{1j}, g_{2j}) = W_{jj}A_{12}$$

$$g_{i\bullet} \sim MVN(0, A_{ii}W), \text{ or } \mathrm{cov}(g_{i1}, g_{i2}) = W_{12}A_{ii}$$

$$e_i \sim MVN(0, V), \text{ or } \mathrm{cov}(e_{i1}, e_{i2}) = V_{12}$$

how: software

- WinQTL/QTL Cartographer: Jzmapqtl
  - Jiang Zeng (1995); statgen.ncsu.edu/qtlcart/
- MultiQTL
  - Korol et al. (2001); www.multiqtl.com
- QTL Express
  - Knott Haley (2000); qtl.cap.ed.ac.uk

Mapping Microarray Data

- overview, wish lists
  - Jansen, Nap (2001); Cheung, Spielman (2002); Doerge (2002); Bochner (2003)
- single gene expression as trait (single QTL)
  - Dumas et al. (2000)
- microarray scan via 1 QTL interval mapping
  - Brem et al. (2002); Schadt et al. (2003)
  - found *cis* and *trans* acting genes
- multivariate and multiple QTL approach
  - Lan et al. (2003)

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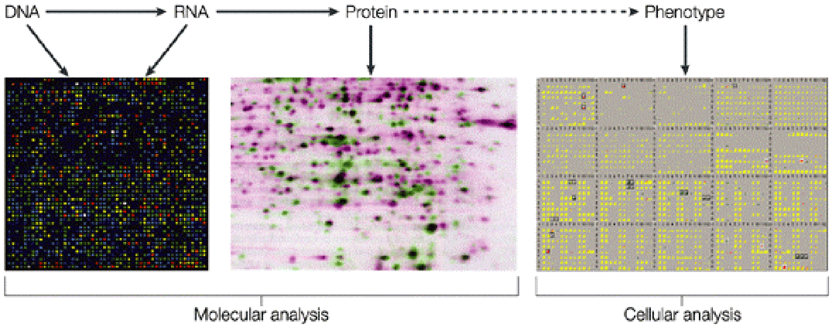
central dogma via microarrays (Bochner 2003)



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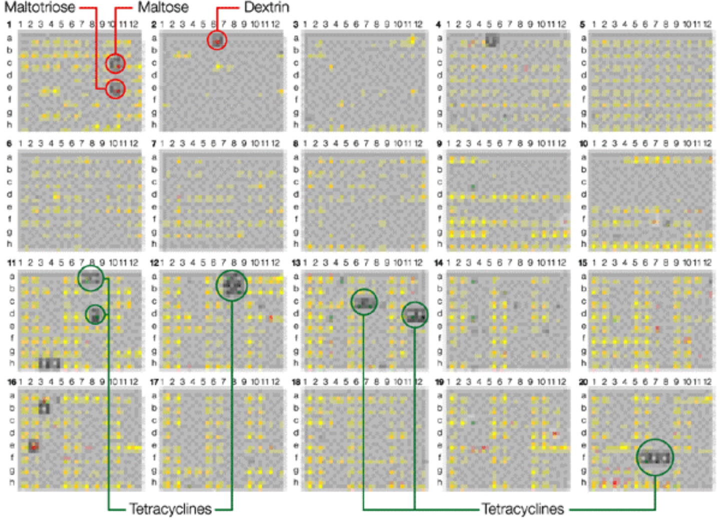
mutant (green) vs. parental (red) E. coli (Bochner 2003)



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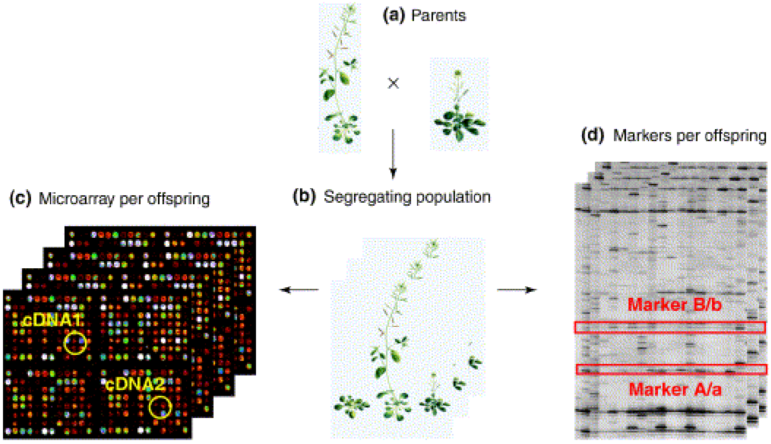
idea of mapping microarrays (Jansen Nap 2001)



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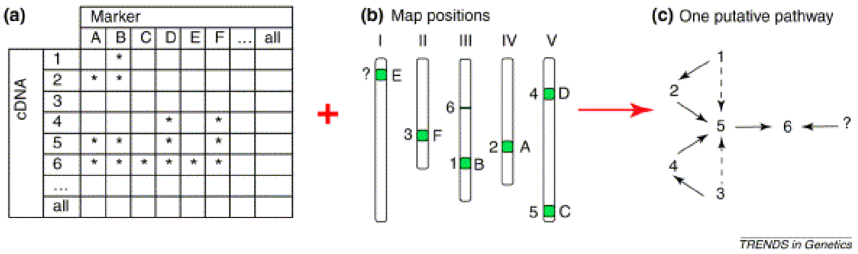
goal: unravel biochemical pathways (Jansen Nap 2001)



(a)

cDNA	Marker A	B	C	D	E	F	…	all
1		*						
2	*	*						
3								
4				*		*		
5	*	*		*		*		
6	*	*	*	*	*	*		
…								
all								

TRENDS in Genetics

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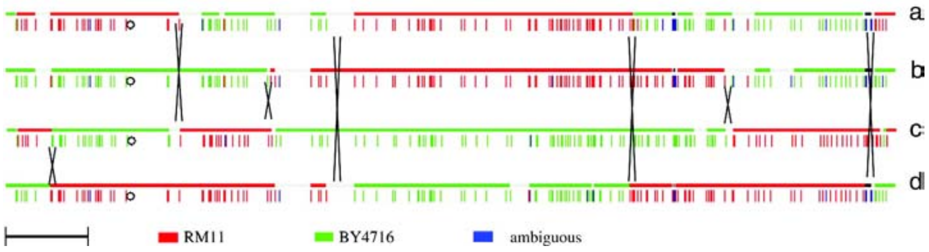
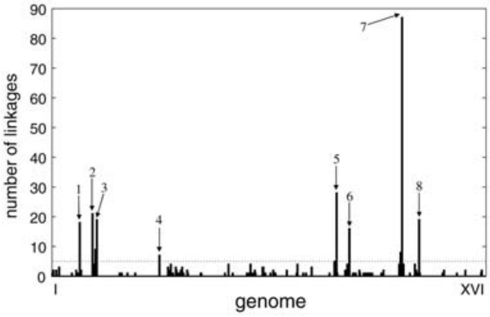
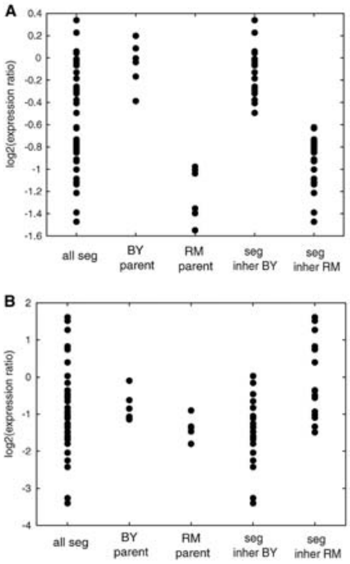
yeast linkage mapping: tetrad analysis (Brem et al. 2002)



QTL mapping of gene expression (Brem et al. 2002)





Schadt et al. (2003): mapping gene expression in mouse genome